American Association of Tissue Banks

The leader in cell and tissue banking for more than a quarter of a century

27th Annual Meeting, August 23-26, 2003, San Diego, California

9154 '02 DEC 23 P3:50

December 23, 2002

BOARD OF GOVERNORS

Officers
President
Samuel H. Doppelt, M.D
President-Elect
Duke Kasprisin, M.D.
Secretary
Charles Sims, M.D.
Treasurer
Henry M Korent
Immediate Past President
Richard J Kagan, M.D
Members-at-Large
Nancy L. Dock, Ph D
Judith E Woll, M D.

Council Chairs
Council of Accredited Tissue Banks
Michael Jeffries
Margery Moogk
Musculoskeletal Council
Michael J Joyce, M D.
Reproductive Council
Russell Bierbaum
Skin Council
Jan L. Pierce
Tissue Bank Council
Diane Wilson

EXECUTIVE OFFICE
Chief Executive Officer
P Robert Rigney, Jr., J D
Executive Director
Jeanne C Mowe

COMMITTEE CHAIRS
Accreditation
Joel Osborne
Bylaws
Russell Bierbaum
Education
Paula Applegate
Ethics
Norman Kalmin, M D.
Finance
Michael J Jeffries
Government Affairs
Richard Russo
International Affairs
Charles Garrison, M D.
Membership
Jan Pierce
Nominating
Michael J Joyce, M.D
Program
Mary Beth Fisk
Public and Professional Relations
Beverly Bliss
Standards
Francis Hornicek, M.D, Ph.D.
Medical Advisory
Richard Hurwitz, M D

Dockets Management Branch (HFA-305)
U.S. Food and Drug Administration
Room 1061
5630 Fishers Lane
Rockville, MD 20852

In Re: ***[Docket No. 02D-0266]***
Draft "Guidance for Industry: Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)"

Dear Madams and Sirs:

The American Association of Tissue Banks [hereinafter referred to as the "AATB" or the "Association"] submits these comments in response to the Food and Drug Administration's (FDA) publication of the above-captioned document. The notice of this draft guidance document appeared in the June 25th issue of the *Federal Register*.

The Association understands that the draft guidance document represents the Agency's current thinking on this topic and has been distributed for comment purposes only. The document is intended to help minimize the risk of possible transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) through deferral of donors with possible exposure to the agents of CJD and vCJD. The draft guidance is for information purposes only and is not intended for implementation at this time.

I. THE INTEREST OF THE AATB

The AATB is a voluntary, professional, scientific and educational organization. The Association was founded in 1976 and is a tax-exempt organization under Section 501(c)(3) of the Internal Revenue Code.

02D-0266 C13

1350 Beverly Road, Suite 220-A • McLean, Virginia 22101 • Web Site: http://www.aatb.org • Phone: 703-827-9582 • Fax: 703-356-2198 • email aatb@aatb.org

The AATB's mission is public health. The Association is dedicated to ensuring that human tissues intended for transplantation are safe and free of infectious disease, of uniform high quality, and available in quantities sufficient to meet national needs.

To further that mission, since 1984, the Association has published the only standards for tissue banks, the AATB's *Standards for Tissue Banking*. This document is the recognized authoritative source for the industry. Beginning in 1986, the AATB initiated a voluntary Accreditation Program to ensure that tissue-banking activities are being performed in a professional manner in compliance with these *Standards*. All of the AATB's institutional members must be re-inspected and re-accredited every three years. The Association's membership currently includes nearly 1,200 individual members and 71 accredited tissue banks engaged in the recovery, processing, storage and distribution of human tissue.

The AATB has consistently and publicly supported balanced governmental regulation aimed at safeguarding human tissues from disease transmission. With the publication of the Agency's first regulations in 1993 [62 *Federal Register* 40,429], the AATB publicly supported the FDA's establishment of interim disease transmission requirements for human tissues. The Association has long advocated and continues to support balanced and reasonable FDA regulation of tissue banking.

The AATB's *Standards* contain extensive requirements for donor screening and testing to ensure safety and to avoid disease transmission. With the exception of ocular tissue, AATB-accredited banks provide most of the commonly used structural tissues for clinical use in the United States. The Association is, therefore, extremely interested in the draft guidance document and its potential effects on the supply of human tissue for transplantation.

Over the years, the AATB has provided useful information to assist the Agency in addressing its public health challenges, most notably disease transmission. The Association has worked with the FDA to develop an appropriate regulatory scheme in this evolving field of medicine. These comments are intended to continue that collegial and cooperative spirit. The AATB also intends to continue to provide constructive criticism and recommendations for regulatory changes where it believes they are warranted.

II. COMMENTS

1. The AATB Supports Several of the FDA's 'Additional Recommendations for Donor Eligibility."

The AATB supports the inclusion of items 1, 2 and 3 of the FDA's proposed "Additional Recommendations for Donor Eligibility" contained in the draft guidance document. These criteria are already included in the AATB's *Standards* as part of the exclusionary "Criteria For Preventing Viral Or Prion-Associated Disease Transmission Through Transplantation of Human Tissue" (Appendix II).

2. Before Implementing the Draft Guidance Document, the FDA Should Work With the AATB and Industry to Develop a Data Gathering Effort to Determine Whether CJD and vCJD Infection Is Present In the Donor Population, the Best Methods for Reducing the Risk of CJD and vCJD Transmission, and the Potential Effects of the Agency's Additional "Recommendations for Donor Eligibility."

Like the oversight of health care in general, federal regulation of tissue banking to reduce the risk of CJD and vCJD transmission should be based on data, facts and science. Without accurate estimates of the volume and types of tissue used and the probability of infectivity from tissue transplants, the Agency is merely taking its "best guess." It is recommending regulation against a "theoretical possibility." In such instances, three things can happen, two of which are counterproductive. Either the Agency's policy accomplishes what it was designed to do, it fails, or it actually creates more harm than existed at the outset.

Everyone associated with this draft guidance document -- the regulators and regulated alike -- want to minimize or even eliminate any possible risk of transmission of CJD and vCJD by HCT/Ps. Several of the FDA's recommendations have been included in the AATB's *Standards* for some time. Safety is a primary concern. Availability is also a primary concern. The challenge is to improve safety while maintaining sufficient availability.

The difficulty in formulating an effective policy at this time is that little information is known about CJD and vCJD in the United States. Consider the following comments from the FDA's draft guidance document:

- "As of January 2002, over 120 vCJD cases have been diagnosed world-wide. To date, indigenous cases have occurred only in the U.K. and France...
- "No cases of vCJD have been identified in the United States (U.S.)...
- "No BSE has been reported to date in U.S. cattle.
- "There are also no published studies regarding the transmissibility of vCJD by HCT/Ps...the transmission of vCJD by blood and blood products, and by most HCT/Ps, is considered a theoretical possibility.
- "We cannot confidently predict the effect of such deferrals on the supply of HCT/Ps, because much less is known about HCT/P donors than about donors of blood and plasma."

This concern about a lack of information was echoed by the FDA's Transmissible Spongiform Encephalopathies Advisory Committee (TSEAC) at it meetings on January 18-19, 2001 and on June 26-27, 2002.

Because of this scarcity of information and data, the AATB recommends that the FDA work with the Association and the tissue-banking industry to develop a data gathering effort before it implements the draft guidance document. This effort could focus on the extent of CJD and vCJD infection in the tissue donor population, the best methods for reducing the risk of CJD and vCJD transmission, and the potential effects of the Agency's additional "Recommendations for Donor Eligibility" on the availability of transplantable tissue.

The AATB believes that several of its accredited banks may already have some data that would be useful to the FDA. The Association is attempting to gather that data and is willing to work with the FDA to design and conduct this data gathering effort.

3. The FDA Should Consider a Tiered Approach and Differentiate Between Tissues Where the Possibility for Transmission is Greater.

The AATB has always supported the FDA's concept for regulating human tissues that was published five years ago, shortly before the agency issued its final regulation. This 1997 publication was entitled, "A Proposed Approach to the

Regulation of Cellular and Tissue-Based Products" [62 *Federal Register* 9721, March 4, 1997]. The document outlined a regulatory framework to provide "a unified approach to the regulation of both traditional and new products."

The new FDA regulatory framework was based on "a tiered approach to cell and tissue regulation." The framework provided:

> "...only the degree of government oversight necessary to protect the public health. For products with limited public health concerns, the new framework allowed flexibility and innovation without an application review process."

With regard to the transmission of CJD and vCJD by HCT/Ps, the following facts were outlined in the FDA's draft guidance document of June 2002:

- "As of January 2002, over 120 vCJD cases have been diagnosed world-wide.

- "Iatrogenic transmission of CJD through transplantation of dura mater allograft and cornea has been reported. There have been more than 114 cases of transmission of CJD by dura mater allograft worldwide, including three in the U.S.

- "The majority of CJD transmissions from dura mater have occurred in Japan since 1985. Japan has at least 67 cases – almost all of these patients were believed to have received dura mater made in a commingled process.

- "Transmission of CJD by ocular tissue have included one definitive case in the United States...

Although there are no reported cases of CJD or vCJD transmission by tissue processed in the United States, the risk – be it theoretical or otherwise – appears to be greater for dura mater and cornea than for other tissues. The Agency itself recognizes this in the draft guidance document where it states:

> "There are greater risks for CJD/vCJD transmission through some HCT/Ps (for example, dura mater and cornea) as compared to blood and blood products...
>
> "For this reason, the transmission of vCJD by blood and blood products, and by most HCT/Ps, is considered a theoretical possibility. Furthermore, the possibility for transmission of vCJD from certain tissues (i.e., cornea and processed dura mater allograft) seems especially likely, since these tissues are already known to have transmitted CJD."

Over the years, on issues concerning viruses, the FDA's screening procedures and algorithms for determining donor suitability have been based on sound scientific principles. The viruses of concern are blood-borne, and blood-borne viruses can contaminate all tissue. Therefore, general donor suitability criteria are appropriate and effective in promoting the public health.

However, the putative agents of CJD and vCJD are not clearly confined to tissue, but they are found in central nervous system tissues. Consequently, any additional screening procedures that utilize current technology need to be tissue specific and not simply used to screen donors generally.

If the FDA implements additional preventive measures to reduce the possible risk of CJD and vCJD transmission by HCT/P, and given the current state of knowledge about that risk, the AATB recommends that the Agency consider a tiered approach and differentiate between tissues where the possibility for transmission is greater (i.e., dura mater). The TSEAC noted this at its June 26-27, 2002 meeting. (See, Quick Summary, Transmissible Spongiform Encephalopathies Advisory Committee Meeting, June 26-27, 2002, page 3.)

To date, all reported cases of CJD and vCJD transmission from tissue transplants involve tissue connected with the central nervous system. In addition, despite the fact that millions of tissue allografts have been transplanted since 1980, there are no reported cases of CJD or vCJD transmission via musculoskeletal, cardiovascular, skin or reproductive tissue transplants. Given the nature of those tissues and how they are processed, there are questions whether these tissues pose any risk of CJD or vCJD transmission.

In his testimony before the FDA's Transmissible Spongiform Encephalopathies Advisory Committee Meeting on June 26, Dr. Paul Brown, a leading expert on CJD and vCJD, said that bone and peripheral tissues are "not likely to be infectious," or that "it exists at very low levels." (See Transcript, Transmissible Spongiform Encephalopathies Advisory Committee Meeting, June 26-27, 2002, page 99 et seq.)

The AATB would, therefore, further recommend that the FDA not impose any additional regulatory requirements on these tissues until there is some evidence that there is a significant risk of CJD or vCJD transmission.

4. *If the FDA Implements These Additional Preventive Measures to Reduce the Risk of CJD and vCJD Transmission, and If the Donor Family Or Other Consenting Person Is Not Familiar With the Donor's Travel History, the Agency Must Accept This As a Negative Response.*

Most of the FDA's additional "Recommendations for Donor Eligibility" concern residence in the United Kingdom (U.K.) and other European countries during specified periods of time. In addition, there are two recommendations dealing with receipt of blood, blood components and bovine insulin in the U.K. since 1980.

These criteria present difficulties for potential tissue donors, because unlike other donors, tissue donors are a cadaveric population. The informed consent for donation, as well as the medical and social histories of the donors, are usually obtained from family members or other persons who can give the consent. These individuals may not know the details of the potential donor's experience. Consequently, trained requestors are more likely to get an "I don't know" response to many of the travel questions. The TSEAC discussed this problem at its June 26-27, 2002 meeting. (See, Quick Summary, Transmissible Spongiform Encephalopathies Advisory Committee Meeting, June 26-27, 2002, page 3.)

Interviews with next-of-kin are not designed to produce data, but to identify risk factors. If the interviews do not identify risk factors, we can only conclude that no known risk factors were uncovered, not that any exist. It is not intellectually sound to try to turn a verbal review into a definitive investigation in which the lack of clear determination becomes a determination of risk and medical fact.

It is obvious that the inclusion of these additional donor eligibility criteria will have a negative effect on the tissue supply. The only question is how big that effect will be. If the FDA intends to treat an "I don't know" response as anything other than a negative response, the consequences could be severe. For that reason, the AATB recommends that the FDA treat an "I don't know" response as a negative response.

III. Conclusion

The AATB thanks the FDA for the opportunity to comment on the draft guidance document. The Association commends and supports the FDA's efforts to prevent the transmission of CJD and vCJD by tissue transplants.

As was said at the outset, the AATB has a long and valued history of working with the Agency to develop an appropriate regulatory scheme in this evolving field of medicine. These comments are intended to continue that collegial and cooperative spirit.

The AATB stands ready and willing to assist the FDA with this draft guidance document in any way that the Agency deems appropriate.

Sincerely,

P. Robert Rigney, Jr., J.D.
Chief Executive Officer

PRRJr/br